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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,340	03/30/2004	Jay A. Berzofsky	015280-368240US	8261

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EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
11/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,340	BERZOFSKY ET AL.	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14,25-35,70 and 71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-14,25-35,70 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4, and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Klavinskis et al. (J. of Immunol., 1996, 157:2521-2527) and either Ahlers et al. (J. of Immunol., 1997, 158:3947-3958) or Berzofsky et al. (WO 94/26785).

The claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting only a rectal mucosal tissue of the subject with a composition comprising a chimeric peptide having the amino acid sequence of SEQ ID NO:9.

Klavinskis et al. teaches rectal and vaginal immunization by administering an SIV peptide antigen covalently linked to cholera toxin B subunit (CTB). CTB was used as an adjuvant. See page 2522 – Immunization schedule. Klavinskis et al. showed that CTLs were isolated from the rectal mucosa and were antigen-specific (see page 2524).

Klavinskis et al. does not teach SEQ ID NO:9 or an antigen from HIV-1 or administering the antigen without an adjuvant. However, both Ahlers et al. and Berzofsky et al. disclose the peptide of SEQ ID NO:9 (see page 3948 of Ahlers et al. and SEQ ID NO:28 and claim 15 of Berzofsky et al.). Both references describe the peptide of SEQ ID NO:9 as being derived from HIV-1, as an inducer of cytotoxic T cells, and useful for therapeutic or prophylactic vaccines against HIV.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis et al. to administer the peptide of SEQ ID NO:9 to a subject. One would have been motivated to do so given the suggestion by Klavinskis et al. that to prevent dissemination of HIV to the regional lymph nodes, an effective vaccine may need to stimulate CTL in the rectal or genital tract (see abstract and introduction). Further, given that the rectal route is a recognized major route for HIV transmission and given that there is a recognized need in the art to raise a mucosal immune response at the site of transmission, it would have been obvious to administer an antigen/construct to the rectal mucosa in order to reduce transmission. One also would have been motivated by the teachings of Ahlers et al. and Berzofsky et al. (SEQ ID NO:9 contains an immunodominant HIV CTL epitope). There would have been a reasonable expectation of success given the findings of Klavinskis et al. that mucosal or targeted

lymph node immunization generates antigen-specific CTL in the rectal and genital mucosa.

As for the use of adjuvants, Klavinskis et al. teaches the use of cholera toxin as an adjuvant. However, it is known in the art that immune responses can be induced with or without adjuvants. Thus, it is well within the purview of one of ordinary skill in the vaccine arts to administer an antigen with or without an adjuvant.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated July 2, 2009, applicants again argue that the claimed invention is directed to administering antigen to only colorectal tissue; whereas, Klavinskis et al. discloses rectal or vaginal administration followed by three oral administrations of the vaccine. All of applicants' arguments have been fully considered, but not found persuasive.

In Klavinskis et al., at the time of administering the antigen to mucosal tissue, rectal or colorectal mucosal tissue was the only site of administration. The oral administrations were carried out months after the rectal administration. Applicants' claims, as currently amended, do not eliminate further antigen administrations at a later time in the future via another route or the same route. Applicants' newly added limitation merely describes what happens at a particular point in time (i.e., at first exposure to the antigen), but does not address what may happen later. According to the claims, at the time of antigen administration (or first exposure to the antigen), the

antigen is administered to colorectal tissue only. Klavinskis et al. teaches this also. Klavinskis et al. goes on to teach oral administrations at monthly intervals (at least 30 days after the first exposure of antigen to rectal mucosa).

As written, applicants' own claims do not exclude subsequent administrations (orally or to mucosal tissue) of the antigen at some time period after the first administration (where only colorectal tissue is exposed to the antigen). Perhaps, applicants should consider defining the complete vaccination schedule (total number of administrations, doses, etc.) to induce an immune response so it is clear that no subsequent administrations may be given.

Claims 1, 5-14, 25-35, 70 and 71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Klavinskis et al. and either Ahlers et al. (J. of Immunol., 1997, 158:3947-3958) or Berzofsky et al. (WO 94/26785) as applied to claims 1, 3, 4, 25 above and further in view of Kiyono et al. (Advanced Drug Delivery Reviews, 18: 23-51).

The claims are drawn to a method for inducing a protective rectal mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprising contacting only a rectal mucosal tissue of the subject with a composition comprising a purified soluble antigen, wherein the method further comprises administering a purified cytokine, e.g., GM-CSF, IL-2, IL-7, IL-12, IFN-γ or TNF-α, to the subject.

The teachings of Klavinskis et al. are outlined above. Klavinskis et al. does not teach administering a cytokine to the subject. However, Ahlers et al. teaches immunizing a subject with the peptide of SEQ ID NO:9 and various cytokines (GM-CSF,

IL-2, IL-12, IFN-γ or TNF-α). Ahlers et al. found that GM-CSF synergized with IL-12 for CTL induction. TNF-α also synergized with IL-12, but by a different mechanism, inducing IFN-γ production, thus shifting the response to a Th1 phenotype (see abstract). Ahlers et al. suggests that in addition to IL-2, optimum induction of CD8+ CTL *in vivo* requires a combination of cytokines, including GM-CSF and IL-12 (steering the Th response toward Th1 cytokines) (see the abstract and the Results section on page 3949).

It would have been obvious to one of ordinary skill in the art to modify the method taught by Klavinskis et al. to also administer cytokines to the subject with the antigen. One would have been motivated to do so given the suggestion by Kiyono et al. that Th cell-derived cytokines are essential for the induction of appropriate antigen-specific mucosal immune responses (see bottom of page 23) and the teachings of Ahlers et al. There would have been a reasonable expectation of success given the findings of Ahlers et al. with regard to CTL induction by cytokines. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated July 2, 2009, applicants argue, *inter alia*, that Ahlers et al. and Berzofsky et al. teach only systemic administration of antigen.

Although Ahlers et al. teaches the co-administration of a cytokine in the context of systemic immunization, it is reasonable for one of ordinary skill in the art to apply the teachings of Ahlers et al. to other administration methods, including mucosal immunizations. One would be motivated to do so because Ahlers et al. found that in addition to 1L-2, optimum induction of CD8+ CTL in vivo requires a combination of cytokines, including GM-CSF and 11-12 (steering the Th response toward Th1 cytokines). Ahlers et al. stated that GM-CSF probably acts to enhance antigen presentation and CD4+ cell help. Because antigen presenting cells are found in both rectal and vaginal mucosa, it would be reasonable for one of ordinary skill in the art to expect cytokines, e.g., GM-CSF, to aid in the induction of CTL and in antigen presentation in the method of Klavinskis et al. where antigen is administered to rectal and vaginal mucosal tissue.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648